Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Voxzogo

Active ingredients: Vosoritide

Sponsor: BioMarin Pharmaceutical Australia Pty Ltd

January 2023

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Aged Care and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety, and efficacy.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
- To report a problem with a therapeutic good, please see the information on the TGA website.

About AusPARs

- The Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ADR	Adverse drug reaction
AE	Adverse event
AGV	Annualised growth velocity
ASA	Australia specific annex
cGMP	Cyclic guanosine monophosphate
CI	Confidence interval
CMI	Consumer Medicine Information
CNP	C-type natriuretic peptide
EMA	European Medicines Agency (European Union)
EU	European Union
FGFR3	Fibroblast growth factor receptor 3
ISR	Injection site reaction
LS	Least squares
NAb	Neutralising antibody
PD	Pharmacodynamic(s)
PI	Product information
PK	Pharmacokinetic(s)
PSUR	Periodic safety update report
RCT	Randomised controlled trial
RMP	Risk management plan
SAE	Serious adverse event
SD	Standard deviation
SDS	Standard deviation score
$t_{1/2}$	Half-life
TGA	Therapeutic Goods Administration

Abbreviation	Meaning
QoL	Quality of life

Product submission

Submission details

Type of submission:	New biological entity
Product name:	Voxzogo
Active ingredient:	Vosoritide
Decision:	Approved
Date of decision:	29 June 2022
Date of entry onto ARTG:	6 July 2022
ARTG numbers:	376616, 376617 and 376618
▼ *Black Triangle Scheme:*	Yes This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia
Sponsor's name and address:	BioMarin Pharmaceutical Australia Pty Ltd 119 Willoughby Road Crows Nest, NSW, 2605
Dose form:	Powder for injection
Strengths:	0.4 mg/vial (reconstituted as 0.4 mg/0.5 mL solution, producing a 0.8 mg/mL concentration) 0.56 mg/vial (reconstituted as 0.56 mg/0.7 mL solution, producing a 0.8 mg/mL concentration) 1.2 mg/vial (reconstituted as 1.2 mg/0.6 mL solution, producing a 2 mg/mL concentration)
Containers:	Vial and pre-filled syringe
Pack size:	10 vials Each pack contains: • 10 vials of Voxzogo (vosoritide), powder for injection • 10 prefilled syringes of diluent (water for injection) • 10 individual single use needles (23 gauge, for reconstitution) • 10 individual single use syringes (30 gauge, for administration)
Approved therapeutic use:	*Voxzogo is indicated for the treatment of achondroplasia in patients 2 years of age and older whose epiphyses are not*

closed. The diagnosis of achondroplasia should be confirmed by appropriate genetic testing.

Route of administration: Subcutaneous injection

Dosage: Treatment with Voxzogo should be initiated and directed by a physician appropriately qualified in the management of growth disorders or skeletal dysplasias. It is important to initiate treatment in children as young as possible.

The volume of Voxzogo to be administered at the recommended dose is based on the patient's weight and the vosoritide concentration.

The usual dose is 15 µg/kg body weight. For practicality reasons and to account for weight-related pharmacokinetic changes (see section 5.2 Pharmacokinetic Properties of the Product Information), the following dosing is recommended in the table below.

Body weight (kg)	**Voxzogo daily injection volume (mL)**		
	0.4 mg/0.5 mL	0.56 mg/0.7 mL	1.2 mg/0.6 mL
10-11	0.30 mL		
12-16		0.35 mL	
17-21		0.40 mL	
22-32		0.50 mL	
33-43			0.25 mL
44-59			0.30 mL
60-89			0.35 mL
≥ 90			0.40 mL

Note: 0.4 mg/0.5 mL corresponds to 0.8 mg/mL; 0.56 mg/0.7 mL corresponds to 0.8 mg/mL, and 1.2 mg/0.6 mL corresponds to 2 mg/mL concentration of vosoritide.

Duration of treatment

Treatment with Voxzogo should be stopped upon confirmation of no further growth potential, indicated by a growth velocity of less than 1.5 cm/year and closure of epiphyses.

Growth monitoring

Patients should be monitored and assessed regularly every 3 to 6 months to check body weight, growth and physical development. Dose should be adjusted according to the patient's body weight (see table above and the Product Information for details).

	For further information refer to the Product Information.
Pregnancy category:	B2 Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage. The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the submission by BioMarin Pharmaceutical Australia Pty Ltd (the sponsor) to register Voxzogo (vosoritide) 0.4 mg, 0.56 mg, and 1.2 mg powder for injection (vial) for the following proposed indication:

> *Voxzogo is indicated for the treatment of achondroplasia in patients 2 years of age and older whose epiphyses are not closed. The diagnosis of achondroplasia should be confirmed by appropriate genetic testing.*

Each vial of vosoritide is intended to be diluted with water for injection (via a supplied prefilled syringe with the intended volume of diluent needed) prior to administration. Each vial, well reconstituted provides the following:

- 0.4 mg/vial, reconstituted as 0.4 mg/0.5 mL solution, corresponding to a vosoritide 0.8 mg/mL concentration;
- 0.56 mg/vial, reconstituted as 0.56 mg/0.7 mL solution, corresponding to a vosoritide 0.8 mg/mL concentration; and
- 1.2 mg/vial reconstituted as 1.2 mg/0.6 mL solution, corresponding to a vosoritide 2 mg/mL concentration)

Achondroplasia is an inherited autosomal dominant condition caused by a gain of function mutation in the fibroblast growth factor receptor 3 gene (*FGFR3*), encoding a negative regulator of chondrocyte proliferation and differentiation in the long bone growth plate. Achondroplasia accounts for more than 90% of disproportionate short stature, or dwarfism, and is characterised by shortening of the proximal part of the arms and legs. Achondroplasia is associated with potentially serious medical complications such as foramen magnum and spinal stenosis, both of which cause increased morbidity and mortality.

Additional clinical characteristics include bowed legs, frontal bossing, macrocephaly with a prominent forehead, midface hypoplasia, narrow chest, trident shaped hands with short fingers, spinal cord compression, otitis media, hearing loss, dental overcrowding, excessive weight gain, severe thoracolumbar kyphosis, and lumbar lordosis. Patients with

achondroplasia suffer from impaired health related quality of life, with decreased physical and mental health scores.

There are currently no pharmacological treatments for achondroplasia registered in Australia, and the only standard treatment is supportive care, which includes devices and occupational therapy to help with the activities of daily living, physical therapy, and surgical interventions to manage medical complications associated with the disease. Due to the risk of potentially serious sequelae, it is important that treatment is sought for complications at an early stage.

Vosoritide was designed to mimic C-type natriuretic peptide (CNP) pharmacological activity by down regulating *FGFR3*-signalling and consequently promoting endochondral bone formation, such that with sufficient duration of treatment, it has the potential to improve the phenotype of individuals with achondroplasia. Vosoritide was developed to be resistant to neutral endopeptidase (NEP) degradation resulting in an extended half-life ($t_{1/2}$) relative to endogenous CNP that increases exposure to the target growth plate and allows for once daily subcutaneous administration to produce its desired pharmacologic effect.

This submission was submitted through the TGA's Comparable Overseas Regulator A (COR-A) process, using evaluation reports from European Medicines Agency (EMA) The full dossier was submitted to the TGA.

Regulatory status

This product is considered a new biological entity for Australian regulatory purposes.

This product received orphan drug designation on 16 June 2021 for the following indication:

> *For the treatment of achondroplasia (ACH).*

At the time the TGA considered this submission, a similar submission had been approved in the European Union on 26 August 2021. A similar submission was under consideration in the United States (submitted on 20 August 2020) and Japan (submitted on 28 September 2021).

The following table summarises these submissions and provides the indications where approved.

Table 1: International regulatory status

Region	Submission date	Status	Approved indications
European Union Rapporteur: Germany Co-rapporteur: Austria	24 July 2020	Approved on 26 August 2021	*Voxzogo is indicated for the treatment of achondroplasia in patients 2 years of age and older whose epiphyses are not closed. The diagnosis of achondroplasia should be confirmed by appropriate genetic testing.* (Approved orphan indication: Treatment of achondroplasia)
United States of America	20 August 2020	Approved on 19 November 2021	*Voxzogo is indicated to increase linear growth in pediatric patients with achondroplasia who are*

Region	Submission date	Status	Approved indications
			5 years of age and older with open epiphyses. This indication is approved under accelerated approval based on an improvement in annualized growth velocity [see Clinical Studies (14)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).
Japan	28 September 2021	Under consideration	Under consideration

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA PI/CMI search facility.

Registration timeline

The following table captures the key steps and dates for this submission.

Table 2: Timeline for Submission PM-2021-04759-1-5

Description	Date
Designation (Orphan)	16 June 2021
Submission dossier accepted and first round evaluation commenced	30 November 2021
First round evaluation completed	22 April 2022
Sponsor provides responses on questions raised in first round evaluation	23 May 2022
Second round evaluation completed	10 June 2022
Delegate's Overall benefit-risk assessment	28 June 2022
Registration decision (Outcome)	29 June 2022
Completion of administrative activities and registration on the ARTG	6 July 2022

Description	Date
Number of working days from submission dossier acceptance to registration decision*	117

*The COR-A process has a 120 working day evaluation and decision timeframe.

Submission overview and risk/benefit assessment

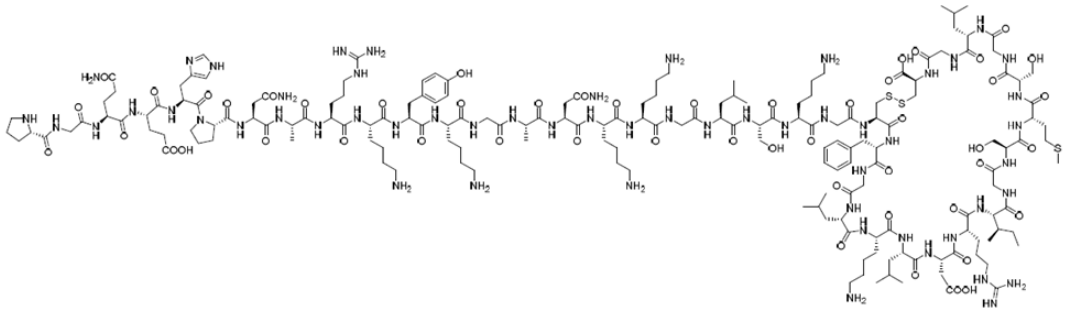
A summary of the TGA's assessment for this submission is provided below.

This section is a TGA summary of wording used in TGA's evaluation report, which discussed numerous aspects of overseas evaluation reports and included some information that was commercial-in-confidence.

Quality

The manufactured drug substance is a recombinant protein made up of 39 amino acids. The structure is shown below in Figure 1. Vosoritide contains C-terminal residues of the native human CNP and two additional proline and glycine residues at the N-terminus. Vosoritide weighs 4100 Daltons (Da) and contains a cysteine disulfide bond forming a cyclical loop and stem structure.

Figure 1: Structure of vosoritide



The vosoritide drug product is a sterile lyophilised powder. This powder is intended for single use following reconstitution with sterile water for injection. Vosoritide drug product is available in three concentrations 0.4 mg per vial, 0.56 mg per vial and 1.2 mg per vial. The reconstituted solution contains a vosoritide concentration of 0.8 mg per mL (for the 0.4 mg and 0.56 mg vials) or 2 mg per mL (for the 1.2 mg vial) of the active substance.

Vosoritide is supplied in a container closure system consisting of a 2 mL clear glass vial closed with a rubber stopper and crimp sealed with flip off aluminium cap.

The proposed shelf life for vosoritide is 24 months when stored at 2 to 8°C. The product may be stored at room temperature below 30°C for a single period of up to 90 days, but not beyond the expiry date. Vosoritide should not be returned to the refrigerator after storage at room temperature. The product should be stored in the original package to protect from light. Freezing should be avoided. The reconstituted solution, if not used immediately, must be administered within three hours.

There are no outstanding issues and no objections on quality grounds to the registration of Voxzogo.

Nonclinical

The nonclinical data support the proposed indication. Vosoritide increased bone growth in healthy animals and disease models. However, bone growth was irregular and resulted in impaired hind limb function, most notably in healthy animals. The potential for this to occur as a result of vosoritide treatment in animal models of disease was less clear, as achondroplasia itself impairs joint and limb function. The potential long-term risks of bone or joint malformations that could lead to osteonecrosis and cartilage dysfunction after longer treatment durations cannot be fully evaluated based on the nonclinical data. According to the overseas regulator, long term safety will be further characterised in the post market setting from ongoing long-term studies and the planned post authorisation safety study. The nonclinical evaluator supports this proposal for post market monitoring.

Safety pharmacology studies did not identify clinically relevant hazards aside from hypotension and tachycardia, which are pharmacological effects of vosoritide. Slight irritation was observed at injection sites in animal studies. Vosoritide is not considered to pose a genotoxic or carcinogenic hazard in humans.

The sponsor has proposed pregnancy category B1.[1] Based on in the low predictive value of the embryofetal studies in rats and rabbits, pregnancy category B2;[2] is recommended.

There are no nonclinical objections to the registration of vosoritide, but it is recommended that the potential for undesired bone and joint effects should be monitored post-market.

Clinical

Pharmacology

Pharmacokinetics

The human pharmacokinetic (PK) properties of vosoritide were assessed in three *in vitro* studies performed using human biomaterials and seven clinical studies.

The sponsor has presented a limited investigation on clinical pharmacokinetics partly owing to the nature of the compound (being a protein), the orphan nature of the disease to be treated, and the difficulties in investigating PK in healthy subjects, with hypotensive effects preventing the administration of higher doses. This is considered acceptable.

The absolute bioavailability of vosoritide is unknown, as only the subcutaneous route was investigated in the clinical studies. While basic parameters of PK (absorption, distribution and other parameters) have been adequately investigated, several aspects of PK investigations and characterisations have been omitted or are partly deficient. The compound has been found to be non-proportional with increased plasma levels at higher doses. Demographic factors appear to play a role with regard to age and weight, however, this is thought to be attributable to weight only, which is likely to also explain the time related effect of increase bioavailability over time (in long term observation).

Only minor changes to formulation were made during the development, therefore no relevant changes in bioavailability are expected, and no comparison between formulations

[1] **Pregnancy category B1**: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.
Studies in animals have not shown evidence of an increased occurrence of fetal damage.

[2] **Pregnancy category B2**: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.
Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.

has been conducted. The interchangeability of administration sites has only partly been investigated, but no relevant differences were detected, and the proposed alteration of administration sites was also mirrored in the development program, it appears that no clinically relevant deviation is expected, and the proposed dosing/administration site is considered acceptable.

In addition, theoretical considerations on metabolism were provided since, as a small peptide, vosoritide is expected to be cleared primarily by protease mediated catabolism, receptor mediated clearance via natriuretic peptide receptor C (NPR-C) and renal elimination. Due to the nature of the compound and its rapid clearance, no further investigations were carried out with regard to identification of further degradants or metabolites and their pharmacodynamic (PD) activity.

The sponsor clarified that endogenous CNP has a short half-life of 2.6 minutes in humans.[3,4] The structural modification of vosoritide confers resistance to proteolysis by neutral endopeptidase such that its half-life is extended almost 10-fold (mean $t_{1/2}$ of 27.9 minutes at Week 52 of Study 111-301) in comparison to endogenous CNP.[5] Furthermore, the sponsor explained that the longer half-life observed during the trials in healthy volunteers might be explainable by the higher body weight of the healthy adult volunteers compared to the paediatric achondroplasia patients. The increased total dose administered to adult healthy volunteers might have saturated clearance and prolonged the elimination half-life. This appears acceptable.

Antibody formation has not shown to have an influence on PK.

Population pharmacokinetic data

A population pharmacokinetic (popPK) analysis for vosoritide was performed with data from 158 patients with achondroplasia (4741 observations finally included from 6181 observations in total) from Study 111-202, Study 111-205, Study 111-206, Study 111-301 and Study 111-302. Data from Study 111-101, a study with 22 healthy male adults was not included because popPK parameters were too different.

The population pharmacokinetics database included data from patients ranging in age from 0.95 to 15 years (mean age was 8.43 years). Weight ranged from 9 kg to 74.5 kg (mean baseline weight was 23.8 kg). Actual daily doses included 2.5 µg/kg/day (six patients), 7.5 µg/kg/day (12 patients), 15 µg/kg/day (151 patients) and 30 µg/kg/day (11 patients).

Model development revealed that vosoritide PK was best described by a one compartment model with first order absorption and first order elimination, when administered by the subcutaneous route. For the final model sex, race, age, location of injection, antidrug antibody (ADA) status and neutralising antibody (NAb) status were tested as covariates but were not significant within the respective dataset.

The underlying confounding effect of weight on clearance was addressed in the proposed weight band posology. In the population pharmacokinetics model, an allometric coefficient was used. Consequently, for dosing allometric scaling is as well considered appropriate. Increased weight and dose of patients (and decreasing clearance per bodyweight) over time during the studies could rather be an explanation for higher plasma concentrations over time. To address the need for a lower per kilogram dose for older patients (higher

[3] Potter, L.R. Natriuretic Peptide Metabolism, Clearance and Degradation, *FEBS J*., 2011; 278 (11): 1008-1817.
[4] Lorget. F. et al. Evaluation of the Therapeutic Potential of a CNP Analog in a *Fgfr3* Mouse Model Recapitulating Achondroplasia, *The American Journal of Human Genetics*, 2012; 97: 1108-1114.
[5] Wendt, D.J. et al. Neutral Endopeptidase-Resistant C-Type Natriuretic Peptide Variant Represents a New Therapeutic Approach for Treatment of Fibroblast Growth Factor Receptor 3-Related Dwarfism, *The Journal of Pharmacology and Experimental Therapeutics,* 2015; 353: 132-149.

bodyweight) and for a higher per kilogram dose for younger patients (lower bodyweight) a weight band based posology was proposed.

The compound is intended for the use in children and adolescents only, and hence, no data on adults and elderly patients are available. The data available for young children proposed for treatment between two and five years of age have been updated from the available results of Study 111-206 and are considered sufficient to be included in the posology. The proposed weight bands are considered acceptable.

The sponsor was requested to revise the posology to make it simpler and alleviate the concern of higher exposure. This revised proposal proposes a weight band dosing which does not include the 15 µg/kg, namely with a 22 to 24 µg/kg and a 18 to 23 µg/kg dose, only for those children of 10 to 11 kg, and 12 to 16 kg body weight, respectively. However, since most of the children reaching the age of two fall in a weight above the two lowest bands and considering the background of higher clearance per kg bodyweight. This dosing in the children under the lowest weight bands was agreed by the overseas regulator. Further data will present with the final data of Study 111-206. The revised posology also addresses the nonlinear effect of weight on clearance. No studies have been conducted in patients with renal or hepatic impairment, based on the nature of the compound and the fact that patients in the intended indication (and age) will rarely suffer from impairment of renal or hepatic function.

Pharmacodynamics

There were no designated pharmacodynamic (PD) studies, but PD markers were assessed as secondary and exploratory endpoints in the clinical studies.

To test PD effects of vosoritide cyclic guanosine monophosphate (cGMP) (as measured in plasma and urine normalised to creatinine) and collagen X (measured in serum) were selected as key biomarkers. Additionally, a clinical PD/efficacy parameter annualised growth velocity (AGV) was evaluated. cGMP reflects activation of the target receptor (natriuretic peptide receptor type B) of vosoritide in the target (growth plate/bones) and off target (for example, vasculature) tissues, and as collagen X is thought to reflect endochondral ossification/bone growth.[6] The AGV parameter is broadly acknowledged and clinically relevant as it directly measures effects of vosoritide on growth. AGV was the key efficacy clinical parameter in all vosoritide studies in achondroplasia patients.

Model based exposure response analyses showed PK/PD dependencies which were consistent with the descriptive PD analysis. All three PD parameters showed correlation between the exposures and effects at the dose levels up to 15 µg/kg. But no correlations were noted at 15 and 30 µg/kg dose levels, that supports the assumption, that there is a saturation of PD effects 15 µg/kg dose.

Since consistent dose and exposure dependent changes were observed across various PD parameters (biomarkers, that is, cGMP, collagen X and clinical parameter AGV) and across the studies, the observed findings are considered reliable and support the use of 15 µg/kg dose of vosoritide in the achondroplasia population greater than or equal to five years of age.

In patients from 2 to less than 5 years of age, only very limited data have been submitted due to the fact that the study is still ongoing and blinded. Study- or age-related differences (age of 2 to less than 5 years old verses older age groups) regarding the exposure response relationship could neither be determined nor excluded based on the presented data.

[6] Coghlan, R.F. et al. A degradation fragment of type X collagen is a real-time marker for bone growth velocity, *Science Translational Medicine,* 2017; 9.

Limited PD data in the 2 to less than 5 years age group and their comparison to older patients suggest that PD effects of vosoritide are similar across various age groups.

The sponsor has not conducted dedicated secondary pharmacology studies, however, evaluations including exposure response relationship for safety relevant parameters, such as heart rate, blood pressure, hypotension, and injection site reactions were conducted and showed no or weak correlation with vosoritide exposure. Overall, based on the data available, there are no concerns raised in regard to potential effects of vosoritide on cardiac QT-interval.[7] Effects of intrinsic/extrinsic factors on PD were assessed as subgroup analyses (sex, age group, Tanner stage,[8] strata, baseline height Z-score, and baseline AGV) in Study 111-301. The results from the subgroup were overall consistent with the main analysis.

Efficacy

Efficacy overview

Studies providing efficacy data

The sponsor provided a comprehensive clinical data package with results from 7 prospective clinical studies as follows:

- Study 111-101-FIM (in healthy volunteers)
- Six studies in subjects with genetically confirmed achondroplasia:
  - Study 111-202 (plus Study 111-205), a dose finding study,
  - Study 111-301 (plus Study 111-302), a pivotal Phase III randomised controlled trial (RCT) in subjects aged 5 years and older up to 18 years of age), and
  - Study 111-206 (plus Study 111-208), a pivotal Phase II RCT (in subjects from the age of zero up to and including those of 5 years of age).

In order to optimise disease characterisation of the untreated population at Baseline and for further comparisons of the long-term outcome, the applicant has performed one observational study, Study 111-901, and generated real world evidence from different natural history sources.

Efficacy assessments and endpoints

The endpoints as well as their assessment during all clinical trials was rather similar, which allows to prove consistency of the outcome and facilitate reliable pooling. Since benefits and risks may differ, younger children below the age of five years were separately investigated after sufficient evidence was generated in those above five years of age.

The efficacy assessment is based mainly on anthropometric measurements. The primary endpoint was the annualised growth velocity (AGV), which was validated and already accepted for the approval for several other growth promoting products. The key

[7] The **QT interval** is the time from the start of the QRS wave complex to the end of the corresponding T wave. It approximates to the time taken for ventricular depolarisation and repolarisation, that is to say, the period of ventricular systole from ventricular isovolumetric contraction to isovolumetric relaxation.
[8] The **Tanner stage**, also known as sexual maturity rating (SMR), is an objective classification system used to document and track the development of a sequence of secondary sex characteristics of children during puberty. For females, Stage 1 occurs after the 8th birthday with no noticeable changes. Stage 2 occurs from ages 9 to 11 with breast 'buds' and pubic hair starting to form. Stage 3 occurs after the age of 12 where acne and armpit hair start to form and height increases at its fastest rate. Stage 4 occurs around age 13 when first period arrives. Stage 5 occurs around the age of 15 where reproductive organs and genitals are fully developed. For males, Stage 1 occurs after the 9th or 10th birthday with no noticeable changes. Stage 2 occurs around the age of 11 with pubic hair starting to form. Stage 3 occurs around the age of 13 where the voice begins to change and muscles get larger. Stage 4 occurs around the age of 14 where acne and armpit hair forms. Stage 5 occurs around the age of 15 when facial hair comes in.

secondary endpoints include height Z-score in order to demonstrate robustness of the primary outcome, as well as 'upper to lower body segment ratio' and 'standing height' as very important endpoints with respect to long term outcome. In addition, several quality of life (QoL) scores and many other endpoints of interest in the target population were included and assessed. Regarding the endpoints assessment, the Type I error was adequately controlled by hierarchical testing.

The inclusion and exclusion criteria used characterise the target population of patients with achondroplasia.

All patients in the clinical program were initially included in the baseline observational growth study (Study 111-901) at least for six months until they could be recruited for one of three studies (and their corresponding extension trials).

Dose finding studies

Study 111-202

Study 111-202 was an open label, dose escalation Phase II study which included 34 subjects with achondroplasia in the age range of 5 to 14 years of age, who received vosoritide daily in doses of 2.5 µg, 7.5 µg, 15 µg and 30 µg subcutaneous in four sequential cohorts of at least eight subjects. Duration was six months, with an optional treatment extension of 18 months. Type I error was adequately controlled by hierarchical testing. After reaching the end of 24 months treatment in Study 111-202, the 30 subjects could be rolled over in the long-term extension Study 111-205. Subjects were followed until reaching near final adult height or a minimum of five years. Subjects in the low dose cohorts were transferred after completion of Study 111-202 into the 15 µg/kg dose cohort to increase the information about the selected posology.

In the dose finding study, Study 111-202, at six months, a significant increase in AGV was observed with vosoritide at 15 and 30 µg/kg. The changes in AGV were dose dependent and achieved plateau with 15 µg/kg, (AGV-median 2.5 µg: -0.146; 7.5 mg: 1.348; 15 µg: 2.652 and 30 µg: 2.899). Since no additional benefit in effect on AGV was seen with 30 µg/kg daily dose compared to 15 µg/kg, the selected dose appears to be adequately justified. The selected dose was further supported by the observed increase in AGV maintained over long term treatment period for Cohorts 3 and 4 in the extension Study 111-205. Moreover, participants initially receiving lower doses in Cohorts 1(2.5 µg/kg dose) and Cohort 2 (7.5 µg/kg dose) transitioned to 15 µg/kg as the selected therapeutic dose during extension and their AGV increased over time, to the level observed with 15 µg/kg. These findings were consistent also if the key secondary endpoint height Z-score was used for assessment.

The once daily regimen was selected because it was expected to yield a maximal treatment effect based on nonclinical evidence. *In vitro* studies demonstrated that a once daily regimen resulted in a similar extent of chondrocyte proliferation relative to twice daily or continuous exposure. This finding is consistent also with respect to the outcome of further pharmacodynamics parameters evaluated.

Efficacy in children aged from 5 to 18 years

Study 111-301

Study 111-301 is a completed multicentre, randomised, double blind, placebo controlled Phase III trial which evaluated the efficacy and safety of 52 weeks of treatment with vosoritide (15 µg/kg daily) compared with placebo in children aged 5 to less than 18 years with a clinical diagnosis of achondroplasia confirmed by genetic testing. Randomisation (in a 1:1 ratio) was stratified by sex and Tanner stage (Tanner stage 1, or Tanner stage greater than 1);[8] with no more than 20% of Tanner stage greater than 1 to be enrolled. A total of 121 subjects were enrolled into the study; 61 subjects were randomised to receive placebo and 60 subjects to receive daily vosoritide 15 µg/kg. After 52 weeks of treatment,

all 61 subjects in the placebo group completed the study and in the vosoritide group, 58 subjects completed, and two subjects withdrew from the study. All subjects were transferred to an extension study (Study 111-302), in which patients were treated with vosoritide until they either attain near final adult height defined as evidence of growth plate closure and six month interval AGV less than 1.5 cm per year AGV or for five years, if near final adult height occurs prior to the end of the five year period.

The initially presented short term analyses of AGV, based on the primary efficacy endpoint in Study 111-301 demonstrates a highly statistically significant improvement in AGV from Baseline to Week 52 (one year) in favour of vosoritide with a least squares (LS) mean difference of 1.57 cm per year (95% confidence interval (CI) 1.22, 1.93, two sided $p < 0.0001$). The improvement in AGV observed at 52 weeks (mean AGV 5.67 cm per year) was maintained after 104 weeks (mean AGV 5.64 cm per year). The maintenance of positive effect on AGV resulted in a continuous improvement in height Z-score, with a change from Baseline of +0.24 standard deviation score (SDS) (LS mean difference of +0.28 (95% CI 0.17, 0.39)) after 52 weeks of treatment and to +0.45 SDS after 104 weeks of treatment. Improvement in the upper to lower body segment ratio was also observed, with a change from Baseline of -0.03 after 52 weeks and -0.09 after 104 weeks of treatment.

The consistency of vosoritide treatment effect in AGV from Baseline to Week 52 (one year) was demonstrated in the pre-specified subgroup analyses for the following subgroups of interest: sex, age group, Tanner stage, strata, baseline height Z-score, and baseline AGV. In addition, these analyses were repeated with the subgroups of race and region showing also a consistent treatment effect.

The comparative analyses on AGV, with follow up of 18 months and two years using an observational/placebo and external control, demonstrated that treatment effect of vosoritide on AGV observed at one year is maintained with continued treatment through Month 18 and two years, as indicated by the consistency of the results.

The magnitude of the effect of vosoritide on AGV (mean difference of 1.57 cm per year) represents restoration of a substantial proportion of the estimated 2 cm per year AGV deficit observed between children with achondroplasia and those with average stature in this age range.[9,10] In the 15 µg/kg analysis population, which allows to assess additional children with longer observation periods are available from all trials the mean (standard deviation (SD)) change from Baseline in AGV to Year 1 was 1.49 (1.62) cm per year and to Year 5 (Month 60) was 1.34 (1.31) cm per year. Considering the 95% confidence intervals, these results allow to presume the absence of clinically relevant tachyphylaxis. Compared to Baseline, the improvement in AGV with vosoritide, was sustained year by year over five years of treatment, in reference to the untreated subjects with achondroplasia at the studied age range, in whom a natural downward trend in AGV is observed (estimated to be 0.2 cm per year) according to the Achondroplasia Natural History database available. These results were supported by the outcome regarding the height Z-Score. Short-term analyses of improvements in height Z-score in terms reported a LS mean difference of +0.28 SDS (95% CI: 0.17, 0.39, $p < 0.0001$) with reference to average stature children and thereby demonstrate consistency to the AGV outcome. In the updated efficacy analysis from Study 111-302 provided during the procedure, consistency of efficacy was demonstrated both, in the initially vosoritide treated population as well as in the newly treated former placebo receiving subjects.

[9] Hoover-Fong, J.E. et al. Age-appropriate body mass index in children with achondroplasia: interpretation in relation to indexes of height, *The American Journal of Clinical Nutrition,* 2008; 88: 364-371.
[10] Kelly, A. et al. Age-Based Reference Ranges for Annual Height Velocity in US Children, *The Journal of Clinical Endocrinology and Metabolism,* 2014; 99: 2104-2112.

Similarly, the durability of the effect of vosoritide was also shown regarding the outcome on height Z-scores in the long term analyses was assessed using natural history comparative analyses on height Z-score at five years, in subjects treated in Study 111-202/205. The relative improvement to placebo in standing height was observed after one year of treatment (LS mean change: 1.57 cm (analysis of covariance model; 95% CI:1.21, 1.93, $p < 0.0001$, Study 111-301) in favour of vosoritide. The long-term increase in height gain, quantifying the sustained and durable effect of vosoritide after five years of treatment versus untreated children with achondroplasia, has been confirmed using an external control in cross sectional and longitudinal analyses using multiple sensitivity methods. These analyses report a baseline adjusted mean difference at five year follow up in cumulative height gain of 9.08 cm (95% CI 5.77, 12.38, $p = 0.0002$) in favour of vosoritide. Although long term data about efficacy during 4 to 5 years is currently restricted on 31 patients from Study 111-205, including 10 patients treated only with vosoritide 15 µg/kg, the regulator acknowledges that the incremental gain in height over five years of treatment was consistent with an approximate 5 time multiple of the gain in height observed in the pivotal Study 111-301 over a one year period. This allows concluding that the positive effect on growth with vosoritide is maintained year by year. However, although the attempts to generate comparative efficacy data for time periods beyond the one year time horizon of the randomised study is methodologically acknowledged and overall reasonable, it needs to be considered that due to inevitable limitations of the underlying data the analyses are considered to be highly exploratory. More comparative data from the ongoing trials and also final height data will become available post-marketing.

The effect on growth has not been associated with accelerated bone maturation, suggesting that final height may indeed be improved. In addition, improvement in linear growth was not associated with an unfavourable effect on body proportion. In fact, the 18 month comparative analysis of upper to lower body segment ratio indicates a trend for a greater decrease in ratio in the vosoritide arm compared to observational/placebo group, suggesting a small positive treatment effect.

The criteria for stopping treatment is in the Section 4.2 of the PI in alignment with the criteria for treatment discontinuation in the open label Study 111-302, as follows:

> 'Treatment with this medicinal product should be stopped upon confirmation of no further growth potential, indicated by a growth velocity of less than 1.5 cm per year and closure of epiphyses.'

Efficacy in children aged 0 to 5 years of age

Study 111-206

Study 111-206 is an ongoing 52 week multicentre, Phase II randomised, double blinded, placebo controlled clinical study. The main objectives of the study are to evaluate the safety of vosoritide and its impact on growth in infants and younger children recruited from birth to 60 months (five years) of age with genetically confirmed achondroplasia. Subjects are or will be enrolled into three age cohorts based on age (Cohort 1: from 24 months of age to less than 60 months (enrolment of or more subjects planned), Cohort 2: from 6 months of age to under 24 months (enrolment of 20 or more subjects planned), Cohort 3: from 0 to less than 6 months (enrolment of 20 or more subjects planned)) starting with the eldest population group. Subjects in the extension trial, Study 111-208 will receive vosoritide until they reached near final adult height. However, this trial was started in June 2018, at the time of data cut-off in September 2019 only 44 of the planned 70 subjects could have been included and enrolled in Cohort 3 which had not commenced yet. Only six patients finalised the 52 week period and could be evaluated regarding efficacy; they were transferred to the extension trial (Study 111-208). Since the study is still ongoing and blinded, only very limited results are currently available.

Efficacy data in the population from 2 to less than 5 years of age from the Phase II trial, Study 111-206 is currently available only for four sentinel subjects in Cohort 1 at time of data cut-off in September 2020. From Baseline to 52 weeks of treatment, these patients experienced a mean (median) increase in height Z-score of 0.34 (0.27), which appears encouraging. At Week 104, two of the three sentinel subjects showed an improvement in the height Z-scores of +0.77 SDS and +0.86 SDS, while an improvement of +0.27 SDS (at Week 78) and +0.20 SDS was noted in the other two subjects. AGV at Week 104 indicated that vosoritide treatment reverted the decline in AGV expected in most of the subjects, with consistent improvement observed over two years of treatment. In addition, the effect appears to be greater in the population younger compared to those older than five years, which is biologically plausible since the maximum growth deficit in children with achondroplasia is accrued before five years of age. There was no worsening in upper to lower body segment ratio, which is clinically important as it indicates that the observed increase in growth is occurring proportionally in both the spine and the lower limbs.

Additional data with a cut-off date of 20 March 2021 were provided for sentinel subjects from Cohort 1. Subjects in Cohort 1 have received vosoritide for a median of 978 days (range: 921 to 1012 days) and the available efficacy data continue to show positive trends across outcome measures.

In addition to the efficacy results available in patients 2 to 5 years, the applicant claims that the extrapolation of efficacy from older to younger children is further supported based on the following elements:

1. The pathophysiology of achondroplasia which is a genetic disorder caused by a single mutation with the underlying pathophysiology of the disease being similar in all age groups.
2. The mechanism of action of vosoritide that directly targets the underlying pathophysiology of achondroplasia by down regulating *FGFR3* signalling.
3. Vosoritide pharmacology, bone specific biomarker response, based on PD marker cGMP and bone specific biomarker serum collagen X, showing the time course and pattern of changes consistent with changes seen in the older children treated with vosoritide.

The sponsor's rationale appears acceptable, the efficacy in children as of two years of age is considered sufficiently demonstrated. However, the ongoing Study 111-206 in this subgroup is important for the collection of additional efficacy data. Submission of final results for Study 111-206 is an imposed condition of registration. Evaluation of health-related quality of life outcomes of vosoritide treatment in the target population remains inconclusive, since no difference was detected between the vosoritide and the placebo groups in the pivotal trial after 52 weeks of treatment. Nevertheless, it is noted that the quality of life assessment was adequately included in all ongoing extension studies.

Safety

Safety data

Safety data from 7 interventional studies have been included with this submission. These are as follows:

- Study 111-101 (dosage of up to 15 µg/kg vosoritide),
- Study 111-202 (dosage of 2.5, 7.5, 15 or 30 µg/kg vosoritide),
- Studies 111-205, 111-206 and 111-208 (dosage of 15 or 30 µg/kg vosoritide), and
- Study 111-301 and Study 111-302 (dosage of 15 µg/kg vosoritide).

Exposure

The Phase II and III clinical studies were considered generally similar in design to justify pooling of the data to facilitate evaluation of long-term safety of vosoritide on the maximum number of subjects with achondroplasia exposed to vosoritide for the longest duration. Three pooled populations were defined to evaluate the safety profile of vosoritide in subjects with achondroplasia:

- All treated population (pooled) includes all subjects with achondroplasia treated with daily vosoritide irrespective of the age or dose received (164 subjects).
- Maximum dosage of 15 µg/kg population includes all subjects with achondroplasia treated with at least one dose of vosoritide but no dose higher than 15 µg/kg daily (148 subjects).
- Pure 15 µg/kg population includes all subjects with achondroplasia aged five years or more treated exclusively with vosoritide at a dosage of 15 µg/kg daily (131 subjects).

Safety can be assessed from 164 subjects with achondroplasia who received treatment (pooled safety population of all treated subjects) of whom 60 subjects were included in the placebo controlled, double blinded, randomised Phase III trial Study 111-301, in subjects in the age range of 5 to 18 years of age.

With respect to the demographic and other baseline factors, it is concluded that the population available reflects adequately the characteristic of the target population. However, the majority of safety data is derived from the population of children between the age of five years or more, up to (and including) children aged 8 years.

Data in younger children aged five years or less at the time of treatment start is restricted to 8 patients, and data in patients aged 15 years or more is restricted to one patient. The use in patients from 2 to 5 years old is listed as missing information in the risk management plan (RMP). Additional data will be available from the still ongoing blinded and randomised Study 111-206, which is an imposed condition to the marketing authorisation and from the corresponding extension trial of Study 111-208.

Overall, it is concluded that the exposure is adequate for the population of subjects 5 years of age or older, as data available also include long-term safety outcome. Nevertheless, more robust long-term safety is needed considering the long-term treatment duration. Long-term safety including skeletal effects as impaired function of extremities and joints and immunogenic potential is listed as missing information in the RMP and additional data will be collected from the ongoing and planned pharmacovigilance activities.

Safety data is available only from the target population since vosoritide was specifically designed to treat patients with achondroplasia.

Adverse events

In the placebo-controlled Study 111-301, the incidence of adverse events (AEs) was similar between the vosoritide (98.3%) and placebo (98.4%) groups, which may allow to conclude with respect to frequency of AEs that the overall toxicity is not significantly increased compared with placebo.

Adverse events reported in the pivotal trial for this submission (Study 111-301) with a 5% or more difference between the vosoritide group compared to placebo and in 5 or more subjects were: injection site reaction (ISR) (73.3% versus 47.5%), injection site swelling (38.3% versus 9.8%), vomiting (26.7% versus 19.7%), arthralgia (15% versus 6.6%), injection site urticaria (13.3% versus 3.3%), blood pressure decreased (11.7% versus 4.9%), diarrhoea (10% versus 3.3%), ear pain, and influenza (10% versus 4.9%).

In the larger pooled safety population, which includes 104 additional patients to those investigated in the pivotal Study 111-301, the frequency of the most commonly AEs were

rather similar: ISR (49.4%), injection site erythema (47%), nasopharyngitis (28.7%), injection site swelling (24.4%), cough (20.1%), headache (20.1%), pyrexia (23.2%), and vomiting (22.6%). Most AEs were Grade 1 (or mild) in severity. Assessment of the details did result in the identification of any relevant or clinically meaningful difference. In the limited data of subjects received a higher dose of 30 µg/kg, no evidence is seen for a clear dose dependency of any of these events.

In the all treated population, the most common treatment-related AEs reported in 10% or more of subjects were injection site reaction (48.8%), injection site erythema (47%), injection site swelling (24.4%), hypotension (11.6%), and injection site urticaria (10.4%). All other treatment-related AEs were reported in less than one subject, apart from injection site related events, were blood pressure decreased (4.9%), vomiting (3%), dizziness (3%), headache (1.8%), fatigue, pre-syncope, and nausea (all 1.2% each).

Adverse events of special interest

In summary, according to the data all injection site reaction type events reported during the study were described as transient, non-serious, and in the majority as mild, resolving without medical intervention. This finding seems to be confirmed by the observation that no subjects discontinued from treatment due to injection site reaction related events.

Decreases of blood pressure were described under the most common adverse drug reactions (ADRs) reported after injection rite reactions (85%) and vomiting (27%). A decrease in blood pressure was observed in 8 patients (13.3 % (11 events)) treated with vosoritide compared to three patients (4.9% (3 events)) in the placebo arm of the pivotal Study 111-301. All events were Grade 1 (mild), and no subject discontinued treatment due to an AE of decrease in blood pressure. The adverse reactions of pre-syncope, syncope, dizziness and fatigue are considered clinically relevant and included as ADRs in Section 4.8 *adverse effects (undesirable effects)* of the PI. Nausea is also included as an ADR as this AE was considered to be a treatment-related AE.

Since vosoritide is a peptide, immunisation and potential hypersensitivity AEs are of special interest with respect to safety. In the placebo-controlled pivotal study (Study 111-301) (131 subjects) the incidence for hypersensitivity AEs was higher in vosoritide group (16 subjects (26.7%) with 81 events) compared to placebo (7 subjects (11.5%) with 13 events).

It is considered reassuring that no Grade 3 or higher events were reported and no subjects experienced events meeting National Institute of Allergy and Infectious Diseases/ Food Allergy and Anaphylaxis Network criteria for anaphylaxis.[11] In conclusion, the risk for the target population due to hypersensitivity AEs can be assessed as mild to moderate, probably also during longer treatment periods as needed.

No deaths occurred in the clinical trials and low rate of serious adverse events is reported with 10 serious AEs in 9 subjects across all Phase II and III vosoritide studies. Three subjects (5%) in the pivotal RCT Study 111-301 experienced four serious AEs in the vosoritide group compared with 4 subjects (6.6%), who experienced five serious AEs in the placebo group. None of these events was assessed as being drug related.

Similar treatment-emergent adverse events and rates were observed also in the updated safety data from the ongoing Study 111-302, particularly in the newly exposed former placebo population from Study 111-301.

[11] Sampson H et al. Second symposium on the definition and management of anaphylaxis: summary report–Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium; 2006. *J Allergy Clin Immunol* 117:391–397

Laboratory findings

With respect to the haematological parameter in the laboratory AEs, slight differences between vosoritide and placebo were noted in favour for placebo. Decreased white blood cell and decreased neutrophils in a number of patients on vosoritide compared to placebo are reported. However, it is acknowledged that the majority of shifts that occurred were self limiting, resolved on or before the next scheduled visit and no haematotoxicity was described in the animal studies. Therefore, these findings are considered unlikely to indicate a safety risk of vosoritide.

In neither the pivotal Study 111-301 nor in the pooled safety population were clinically meaningful changes in the mean values for the other clinical chemistry parameters over time identified with respect to treatment with vosoritide.

Subgroup analyses were not performed in Study 111-301 and only presented for the pooled safety population (all treated pooled group). In these restricted analyses differences in a limited population of 164 patients, safety outcome regarding sex, race/ethnicity groups and geographical regions did not to indicate any reliable difference.

Safety data in subjects with achondroplasia below the age of five years is restricted to 8 patients only. The safety profile in these younger children appears similar to older children, however, no reliable conclusions can be drawn at present. Overall, in the small orphan population the reliability of subgroup analyses may be challenged in general. The use in patients from 2 to 5 years old is listed as missing information in the RMP. Additional data will be available from the ongoing Studies 111-206 and 111-208 in accordance with the agreed RMP.

Immunisation

Since vosoritide is a peptide, immunisation and potential hypersensitivity AEs are of special interest. The effect of anti-vosoritide antibodies was evaluated in the context of reported injection-site reactions, hypersensitivity AEs, and safety impact associated with cross-reactive antibodies. Across the study anti-drug antibodies, responses were detected in approximately 34% to 63% of subjects across studies with the incidence being 38% (59 out of 156) in the all treated population. Neutralising antibodies (NAbs) were detected in 2% (3 out of 156) of all treated subjects at a single visit after which they reverted to NAb negative status at the next time point and remained negative for all subsequent study visits. According to the information available the presence of NAbs in the three subjects had no negative impact on the AGV observed. In general, it appears that the limited immunogenicity results currently available did not indicate a high risk from immunogenicity caused complications.

Discontinuation or treatment interruption due to adverse events

In the pooled safety population 3 subjects (1.8%) discontinued treatment due to an AE. These do not appear to raise any important safety concerns. The proportion of subjects experiencing AEs and serious AEs that led to study drug interruption was balanced between the vosoritide group (10 subjects (16.7%) and 3 subjects (3.3%), respectively) and placebo group (10 subjects (16.4%) and 2 subjects (3.3%), respectively) groups. Thus, it may be seen as an additional confirmation that the vosoritide safety risk profile is mild and differences observed regarding the types of some AEs are explained by the pharmacological effects of the product sufficiently.

From the safety database all the adverse reactions reported in clinical trials have been included in the PI.

Risk management plan

The sponsor has submitted European Union (EU) RMP version 2.0 (date 21 June 2021; data lock point (DLP) 20 November 2019) and Australia specific annex (ASA) version 0.1 (16 August 2021) in support of this application. At round two the sponsor submitted ASA version 0.2 (13 April 2022).

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 3. Further information regarding the TGA's risk management approach can be found in risk management plans for medicines and biologicals and the TGA's risk management approach.

Table 3: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	None				
Important potential risks	None				
Missing information	Long-term safety including skeletal effects as impaired function of extremities and joints and immunogenic potential	✓	✓†‡	–	–
	Use in pregnancy	✓*	–	✓	–
	Use in patients 2-5 years old	✓	✓†§	✓	–

* Targeted follow up questionnaire

† Clinical Study 111-208 and planned post authorisation safety study (PASS) Study 111-603

‡ Clinical Study 111-205 and Study 111-302

§ Clinical Study 111-206

The summary of safety concerns in the ASA aligns with the EU-RMP and is acceptable.

The sponsor has proposed routine pharmacovigilance for all safety concerns. A targeted follow up questionnaire is included for the missing information 'use in pregnancy'. At second round of RMP evaluation, the sponsor has committed to including a field to record Aboriginal and Torres Strait Islander ethnicity. All of the additional pharmacovigilance studies included in the EU-RMP have been included in the ASA. The pharmacovigilance plan is acceptable.

Routine risk minimisation is proposed for the missing information 'use in pregnancy' and 'use in patients 2 to 5 years old'. This aligns with the EU-RMP. Additional risk minimisation is not proposed in the EU-RMP or ASA. The Consumer Medicine Information (CMI) includes instructions for reconstitution and subcutaneous injection. At second round of RMP evaluation, the sponsor confirms inclusion of the CMI document in the product

packaging. The risk minimisation plan in the ASA aligns with the EU-RMP and is acceptable.

There are no new or outstanding recommendations.

Wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The wording suggested by the RMP evaluation is as follows:

> 'The Voxzogo EU-Risk Management Plan (RMP) (version 2.0, dated 21 June 2021, data lock point 20 November 2019), with Australian Specific Annex (version 0.2, dated 13 April 2022), included with submission PM-2021-04759-1-5, and any subsequent revisions, to be revised to the satisfaction of the TGA, will be implemented in Australia.'

The following wording is recommended for the PSUR requirement:

> 'An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).
>
> Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter.
>
> The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.'

As Voxzogo is a new biological entity it should be included in the Black Triangle Scheme as a condition of registration. The following wording is recommended for the condition of registration:

> 'Voxzogo (vosoritide) is to be included in the Black Triangle Scheme. The PI and CMI for Voxzogo must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.'

Risk-benefit analysis

Delegate's considerations

Quality

There are no outstanding quality issues.

Efficacy

The information on vosoritide pharmacokinetics is sufficient overall.

The strength of the clinical development program is adequate since achondroplasia is a rare orphan disease. The sponsor has performed double blinded placebo controlled randomised clinical trials to define efficacy (and safety) adequately.

The dose finding regarding the 15 µg/kg daily dose seems to be adequately justified in children above the age of two years. More study data will be available with the final results from the ongoing Study 111-206.

Vosoritide has been shown to be efficacious in children with achondroplasia from 5 to less than 18 years of age. Data from the pivotal placebo controlled Phase III Studies 111-301 and 111-302, together with the already available long term data in Studies 111-202 and 111-205, demonstrate a consistent statistically significant and clinically relevant efficacy for the primary endpoint AGV. These results are supported by a consistent outcome for the key secondary endpoints height Z-scores as well as standing height. This is illustrated by the highly statistically significant improvement in AGV from Baseline to Week 52 (one year) in favour of vosoritide with a LS mean difference of 1.57 cm per year (95% CI: 1.22, 1.93, two-sided $p < 0.0001$). This suggests that about 75% of the normal growth in the corresponding age could be restored.

Although long-term data about efficacy during 4 to 5 years is currently restricted to 31 patients from Study 111-205, it seems important that the incremental gain in height over 5 years of treatment was consistent with an approximate five time multiple of the gain in height observed in the pivotal Study 111-301 over a one year period. This might allow concluding that the positive effect on growth with vosoritide is maintained long term.

Although, 24 month data from four (eight) sentinel subjects aged 2 to less than 5 years suggest consistent improvement in growth, the placebo-controlled Phase III Study 111-206 (and the extension Study 111-208) are still ongoing and therefore no results are currently available on the randomised groups. The efficacy in this patient subgroup is further supported by extrapolation of the efficacy demonstrated in patients five years and above since the same underlying pathophysiology applies to all age groups and vosoritide acts as a disease modifier the same way across all age groups. In addition, vosoritide pharmacology with bone-specific biomarker response has shown time course and pattern of changes in younger children consistent with changes seen in the older children treated with vosoritide. Therefore, and because early treatment is likely to maximise patient benefit, it appears reasonable to include patients from the age of 2 years in the authorised indication. The final results from the ongoing Study 111-206 in this subgroup will provide more supporting data.

Safety

Vosoritide has an acceptable safety profile and treatment is generally well tolerated from the available clinical development safety data. No signal for additional safety risk in human was identified during the clinical development.

The main adverse reactions identified during the clinical development are related to injection site reactions, blood pressure decrease, vomiting, nausea, fatigue and increased alkaline phosphatase. The available data did not indicate that the improvements in growth is associated with any detectable premature bone maturation, disproportionate skeletal growth or abnormal bone morphology. Moreover, there was no evidence suggestive of any off target effects including renal or central nervous system. The limited immunogenicity results currently available did not indicate a high risk from immunogenicity caused complications.

The sponsor has applied for the treatment of children with achondroplasia above the age of two years. However, currently safety in the population of children with achondroplasia in the age range of between 2 to 5 years can be only assessed from four sentinel patients. Although exposure in the now presented updated safety report was significantly higher and the preliminary data presented seems to indicate no differences regarding the observed adverse events and safety risks from the pivotal Studies 111-206 and 111-208, the data is still limited. Use in patients aged from 2 to 5 years is listed as missing

information in the RMP. Additional information will be collected from the ongoing Study 111-206 which is imposed as a condition of registration and from two additional post-marketing studies (ongoing long term Study 111-208 and planned post authorisation safety study).

Proposed action

Overall, the Delegate considers that the benefit-risk balance of Voxzogo is favourable for the proposed indication.

Advisory Committee considerations

The Delegate did not refer this submission to the Advisory Committee on Medicines for advice.

Outcome

Based on a review of quality, safety, and efficacy, the TGA approved the registration of Voxzogo (vosoritide) 0.4 mg, 0.56 mg, and 1.2 mg powder for injection (vial);[12] indicated for:

> *Voxzogo is indicated for the treatment of achondroplasia in patients 2 years of age and older whose epiphyses are not closed. The diagnosis of achondroplasia should be confirmed by appropriate genetic testing.*

Specific conditions of registration applying to these goods

- Voxzogo (vosoritide) is to be included in the Black Triangle Scheme. The PI and CMI for Voxzogo must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.
- The Voxzogo EU-Risk Management Plan (RMP) (version 2.0, dated 21 June 2021, data lock point 20 November 2019), with Australian Specific Annex (version 0.2, dated 13 April 2022), included with submission PM-2021-04759-1-5, and any subsequent revisions, to be revised to the satisfaction of the TGA, will be implemented in Australia.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

  Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of the approval letter.

  The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

[12] Each vial of vosoritide is intended to be diluted with water for injection (via supplied prefilled syringe) prior to administration to provide the following:
• 0.4 mg/vial, reconstituted as 0.4 mg/0.5 mL solution, corresponding to a 0.8 mg/mL concentration;
• 0.56 mg/vial, reconstituted as 0.56 mg/0.7 mL solution, corresponding to a 0.8 mg/mL concentration; and
• 1.2 mg/vial reconstituted as 1.2 mg/0.6 mL solution, corresponding to a 2 mg/mL concentration.

- When available, the sponsor should submit the final results of the Study 111-206, to further evaluate and support the efficacy and safety of vosoritide in patients aged 2 to 5 years.
- The sponsor should inform TGA of any status or PI changes (especially in patients aged 2 to 5 years) including for the comparable overseas regulators based on Study 111-206 or from the missing information as listed in the RMP.

Laboratory testing & compliance with Certified Product Details (CPD)

- All batches of Voxzogo supplied in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).

  When requested by the TGA, the Sponsor should be prepared to provide product samples, specified reference materials and documentary evidence to enable the TGA to conduct laboratory testing on the Product. Outcomes of laboratory testing are published biannually in the TGA Database of Laboratory Testing Results http://www.tga.gov.au/ws-labs-index and periodically in testing reports on the TGA website.

Certified Product Details

- The Certified Product Details (CPD), as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM) http://www.tga.gov.au/industry/pm-argpm-guidance-7.htm, in PDF format, for the above products should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.

Attachment 1. Product Information

The PI for Voxzogo approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA PI/CMI search facility.

Therapeutic Goods Administration

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